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(54) Title: 5-HT_3 RECEPTOR ANTAGONISTS FOR TREATMENT OF COUGH AND BRONCHOCONSTRICTION

(57) Abstract

A method of treatment of cough and/or bronchoconstriction in mammals, including humans, which method comprises the administration to the mammal in need of such treatment, an effective amount of a 5-HT_3 receptor antagonist.

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5-HT_3 receptor antagonists for treatment of cough and bronchoconstriction.

This invention relates to a method of treatment of cough and/or bronchoconstriction in mammals, including humans, and to the use of compounds in the preparation of a medicament for the treatment of cough and/or bronchoconstriction.

GB 2125398A, EP-A-200444, EP-A-247266, EP-A-235878, EP-A-67770, EP-A-158265, EP-A-158532 and EP-A-254584 disclose classes of compounds which are 5-HT_3 receptor antagonists, useful in the treatment of inter alia migraine, cluster headache and trigeminal neuralgia. GB 2153821A describes a further class of $5HT_3$ receptor antagonists.

It has now been discovered that $5HT_3$ receptor antagonists, such as certain of the above classes of compounds, are of potential use in the treatment of cough and/or bronchoconstriction, such as that arising as a result of asthma.

Cough is useful when it effectively expels secretions i.e. when it is a productive cough. Dry or unproductive cough has no useful effect. Unproductive cough may arise from effects such as cancer (primary or secondary) affecting sensory nerves in the larynx or larger bronchi, from asthma - especially childhood asthma - and in the early or later stages of coryza. Unproductive cough may also occur due to infiltration of the cough centre in the brain by tumour. Cough may also occur without known cause.

Treatment of cough by drugs is unsatisfactory.

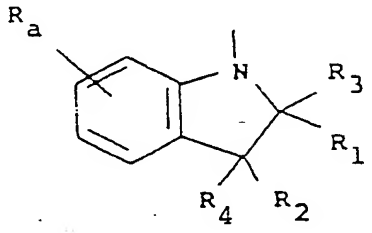
Peripheral stimulation of sensory nerves in the larynx (which can cause cough) can be blocked by local anaesthetics such as lignocaine, but the only effective form of therapy for dry and painful cough used clinically is provided by the opiates (morphine, codiene, and methadone etc.).

Accordingly, the present invention provides a method of treatment of cough and/or bronchoconstriction in mammals, including humans, which method comprises the administration to the mammal in need of such treatment, an effective amount of a 5-HT_3 receptor antagonist, such as a compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof:

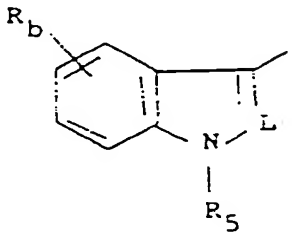
X-CO-Y-Z (I)

wherein

X is a group of formula (a), (b), (c), (d) or (e):



(a)



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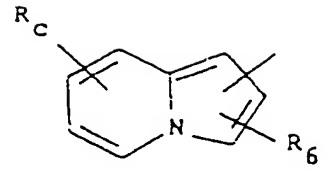

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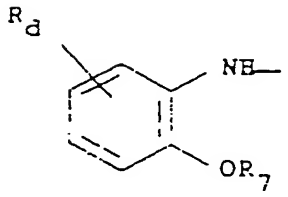

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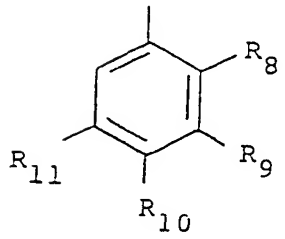


(e)

wherein

R_a to R_d are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or

R_1 and R_2 together are a bond;

R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and

R_4 together with R_2 may be C_{2-7} polymethylene when R_1 is hydrogen;

either R_8 is C_{1-6} alkoxy;

R_9 is hydrogen;

R_{10} is amino or C_{1-7} alkanoylamino; and

R_{11} is halo or C_{1-6} alkylthio; or

R_8 is hydrogen;

R_9 is halo, C_{1-6} alkoxy or C_{1-6} alkyl;

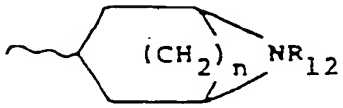
R_{10} is hydrogen or C_{1-6} alkoxy; and

R_{11} is halo, C_{1-6} alkoxy or C_{1-6} alkyl;

L is CH or N;

Y is NH or O, with the proviso that Y is NH when X is (e) and R_8 is C_{1-6} alkoxy;

Z is a group of formula (f), (g) or (h):



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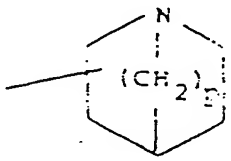

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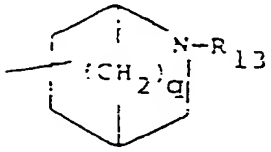


(h)

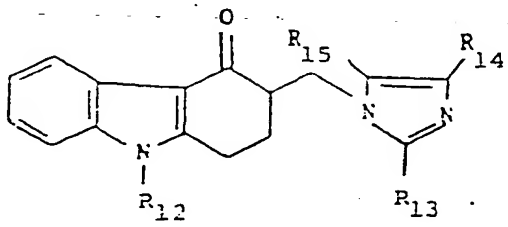
wherein

n is 2 or 3;

p and q are independently 1 to 3; and

R_{12} or R_{13} is methyl or ethyl;

and with the proviso that, when Ar is of formula (b) and Y is -NH-, Z is a group of formula (d) or (e);



(II)

wherein

R_{12} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl-C_{1-3} alkyl; and

one of the groups represented by R_{13}, R_{14} and R_{15} is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-C_{1-3} alkyl and each of the other groups, which may be the same or different, is hydrogen or C_{1-6} alkyl.

In formula (I):

Examples of moieties in alkyl or alkyl containing groups in R_1 to R_{11} include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, preferably methyl.

Suitable examples of R_2 and R_4 when joined include C_2, C_3, C_4, C_5 or C_6 polymethylene, preferably C_2, C_3, C_4 or C_5 polymethylene.

R_a to R_d are preferably selected from hydrogen, fluoro, chloro and hydroxy, most preferably hydrogen. R_b may be 5-, 6- or 7-chloro or fluoro.

When X is of sub-formula (a), R_1 and R_3 are preferably both hydrogen and one or both of R_2 and R_4 (most preferably both) are alkyl groups, such as methyl, or are joined to form C_{2-7} polymethylene; or when one of R_2 and R_4 is hydrogen, the other is preferably ethyl or n- or iso- propyl.

When X is of sub-formula (b), R_5 is preferably hydrogen or a methyl or ethyl group.

When X is of sub-formula (c), one of CO-Y-Z and R_6 is attached at the 1-position and the other is attached at the 3-position as depicted in sub-formula (c), and R_6 is preferably methyl or ethyl.

When X is of sub-formula (d), R_7 is preferably methyl.

When X is of sub-formula (e), and R_8 is C_{1-6} alkoxy, R_8 is preferably methoxy, R_{10} is preferably amino and R_{11} is preferably chloro or bromo, most preferably chloro.

When X is of sub-formula (e), and R_8 is hydrogen, R_9 and R_{11} are preferably chloro or methyl and R_{10} is preferably hydrogen.

X is preferably a group of formula (b) and L is preferably N.

Y is preferably NH.

When Z is a group of sub-formula (f), n is 2 or 3, preferably 3 when X is of sub-formula (b) wherein L is N.

When Z is a group of sub-formula (g) or (h), p and q are preferably 1 or 2.

In formula (II):

It will be understood that when R_{12} represents a C_{3-6} alkenyl group, the double bond may not be adjacent to the nitrogen atom.

The alkyl groups represented by R_{12}, R_{13}, R_{14} and R_{15} may be for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl, methylprop-2-yl, pent-3-yl or hexyl.

An alkenyl group may be, for example, a propenyl group.

A phenyl-C_{1-3} alkyl group may be for example, a benzyl, phenethyl or 3-phenylpropyl group. A cycloalkyl group

may be, for example, a cyclopentyl, cyclohexyl or cycloheptyl group.

The pharmaceutically acceptable salts of the compounds of the formulae (I) and (II) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, lactic, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formulae (I) and (II) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

Pharmaceutically acceptable salts also include quaternary derivatives, examples of which include the compounds quaternised by compounds such as R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Pharmaceutically acceptable salts also include internal salts such as pharmaceutically acceptable N-oxides.

The compounds of the formulae (I) and (II), and their pharmaceutically acceptable salts may also form

pharmaceutically acceptable solvates, such as hydrates which are included whereever a compound of formula (I) or (II), or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formulae (I) and (II) have chiral or prochiral centres, and thus are capable of existing in a number of stereoisomeric forms, including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

Compounds of the formulae (I) and (II) and their salts may be prepared in accordance with the methods described in the aforementioned Patent Publications. Examples of interest include the compounds within formulae (I) and (II) which are specific examples in the aforementioned patent publications. Particular examples include the following compounds:

i) The compound of Example 5 of EP-A-247266.

ii) The compound of Example 6 of EP-A-200444 (BRL 43694A).

iii) The compound of Example A-2 of GB 2125398A (ICS 205-930).

iv) The compound of Example 1 of EP-A-67770 (MDL 72222).

v) The compound of Example 1a of GB 2153821A (GR 38032F).

The administration of the 5-HT_3 receptor antagonist may be by way of oral or parenteral administration; or by inhalation.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.1 to 100mg for example 0.2 to 50mg, of the compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0002 to 5 mg/kg/day, more usually 0.0004 to 2.5 mg/kg/day. In the case of the preferred compounds of the invention, the dose range is 0.0002 to 0.3 mg/kg/day.

No adverse toxicological effects are indicated at the aforementioned dosage ranges.

It is preferred that the 5-HT_3 receptor antagonist is administered in the form of a unit dose pharmaceutical composition in which is combined with a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a

surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions of this invention may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, preferably less than 10 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; xanthine derivatives such as theophylline and aminophylline and corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

The present invention also provides the use of a 5-HT_3 receptor antagonist, such as compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in the treatment of cough and/or bronchoconstriction in mammals, including humans. Such treatment may be carried out in the manner as hereinbefore described.

The present invention further provides a pharmaceutical composition for use in the treatment of cough and/or bronchoconstriction which comprises an effective amount of a 5-HT_3 receptor antagonist, such as compound of formula (I) or (II), or a pharmaceutically acceptable

salt thereof, and a pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

The following clinical tests illustrate the invention.

Compound E6 is the Compound of Example 6 of EP-A-200444, N-(endo-9-methyl-9-azabicyclo-[3.3.1]non-3-yl)-1-methyl-indazole-3-carboxamide monohydrochloride.

Clinical Tests

1. Experimental cough in man can be induced by inhalation of capsaicin (the active ingredient of pepper) and coughing occurs in a dose related manner. Administration of compound E6 intravenously at doses up to 60 µg/kg is found to block capsaicin induced cough.

2. Bronchoconstriction in man can be induced by inhalation of capsaicin (the active ingredient of pepper) or by inhalation of sulphur dioxide. Administration of compound E6 intravenously at doses of up to 60 µg/kg is found to block capsaicin or sulphur dioxide induced bronchoconstriction.

Claims

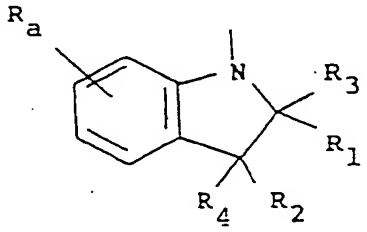
1. A method of treatment of cough and/or bronchoconstriction in mammals, including humans, which method comprises the administration to the mammal in need of such treatment, an effective amount of a 5-HT_3 receptor antagonist.

2. A method according to claim 1 wherein the 5-HT_3 receptor antagonist is a compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof:

X-CO-Y-Z (I)

wherein

X is a group of formula (a), (b), (c), (d) or (e):



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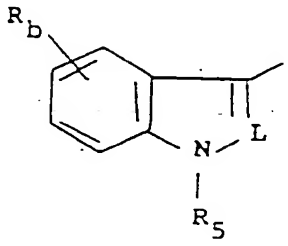

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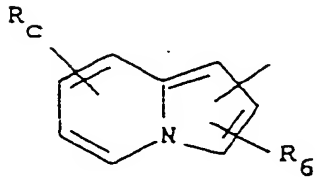

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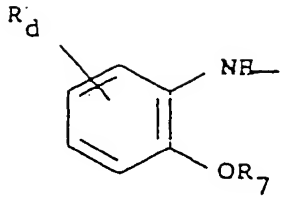

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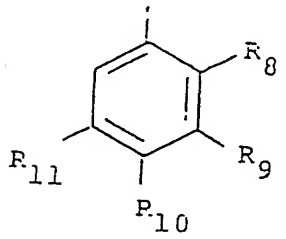


(e)

wherein

R_a to R_d are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or

R_1 and R_2 together are a bond;

R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and

R_4 together with R_2 may be C_{2-7} polymethylene when R_1 is hydrogen;

either R_8 is C_{1-6} alkoxy;

R_9 is hydrogen;

R_{10} is amino or C_{1-7} alkanoylamino; and

R_{11} is halo or C_{1-6} alkylthio; or

R_8 is hydrogen;

R_9 is halo, C_{1-6} alkoxy or C_{1-6} alkyl;

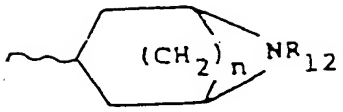
R_{10} is hydrogen or C_{1-6} alkoxy; and

R_{11} is halo, C_{1-6} alkoxy or C_{1-6} alkyl;

L is CH or N;

Y is NH or O, with the proviso that Y is NH when X is (e) and R_8 is C_{1-6} alkoxy;

Z is a group of formula (f), (g) or (h):



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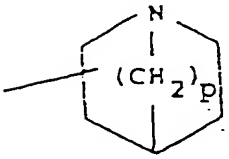

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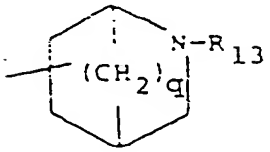


h)

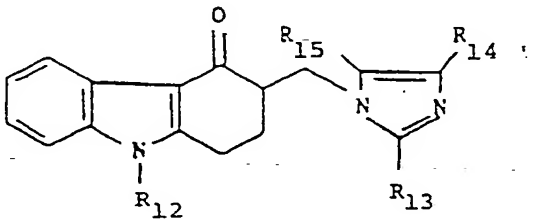
wherein

n is 2 or 3,

p and q are independently 1 to 3; and

R_{12} or R_{13} is methyl or ethyl;

and with the proviso that, when Ar is of formula (b) and Y is -NH-, Z is a group of formula (d) or (e);



(II)

wherein

R_{12} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl-C_{1-3} alkyl; and

one of the groups represented by R_{13}, R_{14} and R_{15} is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-C_{1-3} alkyl and each of the

other groups, which may be the same or different, is hydrogen or C_{1-6} alkyl.

3. A method acccording to claim 2 wherein the compound of formula (I) is the compound of Example 5 of EP-A-247266.

4. A method according to claim 2 wherein the compound of formula (I) is BRL 43694A.

5. A method according to claim 2 wherein the compound of formula (I) is ICS 205-930.

6. A method according to claim 2 wherein the compound of formula (I) is MDL 72222.

7. A method according to claim 2 wherein the compound of formula (II) is GR 38032F.

8. Use of a 5-HT_3 receptor antagonist as defined in any one of claims 1 to 7 in the preparation of a medicament for use in the treatment of cough and/or bronchoconstriction in mammals, including humans.

9. A pharmaceutical composition for use in the treatment of cough and/or bronchoconstriction, which comprises an effective amount of a 5-HT_3 receptor antagonist, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00994

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/415; 31/435; 31/445; 31/46; 31/55

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	J. Physiol. (London), vol. 365, 1985, (GB) D.J. Armstrong et al.: "MDL 72222 (a 5-HT antagonist) antagonizes the pulmonary depressor and respiratory chemoreflexes evoked by phenylbiguanide in anaesthetized rabbits" page 104P, see page 104P	8,9
A	Br.J. Pharmacol., vol. 87, no. 2, February 1986 The Macmillan Press Ltd; H.E. Connor et al: "5-carboxamidotryptamine is a selective agonist at 5-hydroxytryptamine receptors mediating vasodilatation and tachycardia in anaesthetized cats" pages 417-426, see the abstract	8,9
A	Chest, vol. 92, no. 5, November 1987 M. Cazzola et al.: "Ketanserin, a new blocking agent of serotonin S_2-receptors	8,9

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* Special categories of cited documents: [12]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10th February 1989	09 MAR 1989

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	Respiratory functional effects in chronic obstruction of the airways" pages 863-866, see the abstract --	
A	Allgemeine und Spezielle Pharmakologie und Toxikololgie, 3rd Edition, Bibliographisches Institut, Mannheim (DE) 1980, page 151 see page 151	8,9

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 1-7, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT-rule 39.1 (iv): methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.